CONTINUING MEDICAL EDUCATION

The Diagnosis and Treatment of Deep Infiltrating Endometriosis

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SUMMARY

Background: Endometriosis and adenomyosis uteri are the most common benign disorders affecting girls and women after uterine myomas (fibroids), with a prevalence of roughly 5% to 15%. There have been many advances in diagnostic assessment and in our understanding of the disease over the past decade. Steady improvements in treatment have been accompanied by heightened consciousness of the diagnosis among the affected women and the doctors who care for them.

Methods: A selective literature search was carried out in the Cochrane and PubMed databases using the key words "endometriosis," "deep infiltrating endometriosis," "endometriosis AND diagnostics," "endometriosis AND surgical therapy," "endometriosis AND endocrine treatment," and others. The AWMF and ESHRE guidelines were also taken in account.

Results and Conclusion: The main manifestations are primary or secondary dysmenorrhea, bleeding disturbances, infertility, dysuria, pain on defecation (dyschezia), cycle-dependent or (later) cycle-independent pelvic pain, nonspecific cycle-associated gastrointestinal or urogenital symptoms. Cycle-associated problems of urination and/or defecation that are due to endometriosis are most common in young, premenopausal women. Whenever such manifestations are present, endometriosis should be considered in the differential diagnosis, and evidence for it should be sought in the clinical history, physical examination, and ultrasound findings. If endometriosis is histologically confirmed and is of the deeply infiltrating kind, the recommended management today is to refer the patient to an endometriosis center.

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Endometriosis is a disease of the uterus in which tissue from the uterine cavity becomes implanted in the abdominal cavity and, rarely, metastasizes to organs at a distance from the uterus. Endometriosis tissue is biologically the same as basal endometrial tissue. Foci of endometriosis consist of glands, stroma cells, and smooth muscle; they are supplied by nerves (neurogenesis), lymphatic vessels, and blood vessels (angiogenesis) (1–5). Endometriosis cells express estrogen receptors (ER α/β) and progesterone receptors (PR A/B) and therefore respond to endocrine treatments (6, 7). Although endometriosis is considered a disease of women of child-bearing age, its occasional occurrence before the menarche has been histologically documented (4, 8). Postmenopausal endometriosis accounts for less than 3% of cases.

The German-language medical literature uses Latin terms to classify endometriosis by site: "endometriosis genitalis interna" is the name given to adenomyosis uteri, while "endometriosis genitalis externa" designates disease in the internal female genital tract and "endometriosis extragenitalis" designates disease elsewhere, e.g., in the appendix, the bowel, the urinary bladder, the ureter, the vagina, the lung, the liver, the umbilicus, and other, rare locations. Other classification schemes simply speak of peritoneal, ovarian, and deep infiltrating endometriosis. Any manifestation of endometriosis that is located other than in the superficial tissues of the rectovaginal septum and vaginal fornix, the pelvic wall, parametrium, bowel, uterus, or urinary bladder can be called deep infiltrating endometriosis. Endometriosis is currently staged according to the system of the American Society of Reproductive Medicine (ASRM) and the experimental ENZIAN classification.

Definition

Endometriosis is a disease of the uterus in which tissue from the uterine cavity becomes implanted in the abdominal cavity.

Learning objectives

The learning objectives of this article are

- to describe the main manifestations of endometriosis,
- to present the diagnostic evaluation and classification of endometriosis, and
- to give an overview of the available curative and palliative treatment options.

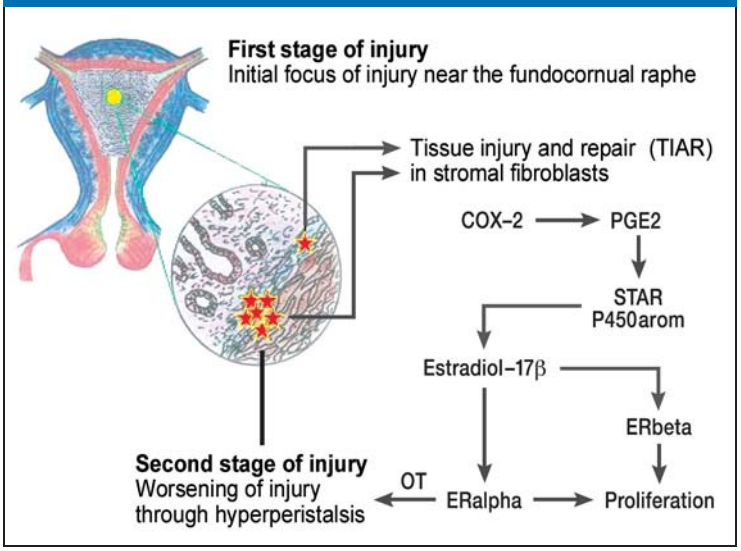
Epidemiology

The estimated prevalence of endometriosis is 5% to 15% among all women of child-bearing age; its prevalence is higher in some subgroups (2, 4, 6). 20% to 48% of women suffering from infertility have endometriosis. Among young women with chronic pelvic pain that does not respond to hormonal therapy or to treatment with nonsteroidal anti-inflammatory drugs (NSAID), the prevalence of endometriosis is roughly 70% (4). No robust data are available concerning the prevalence of deep infiltrating intestinal endometriosis, or of endometriosis of the urinary tract. Ureteric endometriosis, for example, has been described in 0.1% to 0.4% of all cases of endometriosis, while the overall prevalence of urogenital endometriosis is said to be 1% to 2% of the overall prevalence of endometriosis (9, 10).

Etiology

According to the transplantation hypothesis, viable endometrial cells enter the abdominal cavity through retrograde menstruation and become implanted there (11). In what is called retrograde menstruation, the patient bleeds from the vagina during her menstrual period, but menstrual blood also simultaneously enters the abdominal cavity by way of an open Fallopian tube. This hypothesis fails to explain why endometriosis does not affect all women, because all women are thought to have retrograde menstruation. An answer is supplied by the currently favored etiological hypothesis for endometriosis, which is known as the tissue injury and repair (TIAR) concept (7). Embryologically speaking, the uterus is made up of the archimetra (the endometrial glands and stroma and the subvascular layer) and the neometra (the vascular and supravascular layers) (6, 7). The archimyometrium is seen on ultrasonography as a hypodense halo, and on magnetic resonance imaging (MRI) as a hypointense junctional zone, i.e., a layer that is distinct from the normal endometrium (2, 7). Microtrauma can occur at the interface between different layers of uterine tissue, e.g., in the region of the fundocornual raphe, as a consequence of the estrogen-driven increase in peristalsis (7). The repair mechanisms that then come into play are associated with local hyperestrogenism because of aromatase overexpression; they lead, therefore, to paracrine-estrogen-induced uterine hyper- and dysperistalsis, with desquamation and dislocation of the basal endometrium through the Fallopian tubes and out into the abdominal cavity *(Figure 1)* (4, 7). On the other hand, cells of the basal layer can also continually infiltrate the myometrium, giving rise to the fully developed clinical picture of uterine adenomyosis. Endometriosis and adenomyosis are two sides of the same coin (1, 6, 7). There are likely to be stem cells in the basal endometrial layer that play an essential role both in the cyclical regeneration of eutopic endometrial tissue and in endometriosis (12). At present, findings from the fields of

FIGURE 1



According to the concept of tissue injury and repair, the uterus develops from the interacting tissues of the archimetra and the neometra (7). With the onset of ovarian function, uterine contractility increases, with ensuing tissue injury in the region of the fundocornual raphe. The repair processes that come into play in the basal layer of the endometrium cause local hyperestrogenism, which, in turn, leads to uterine dysperistalsis. A vicious circle arises, in which endometrial tissue is either sloughed off (transtubal transport, leading to endometriosis) or else undergoes intensified proliferation, penetrating into the myometrium (the beginning of adenomyosis). The illustration is reproduced with the kind permission of Prof. Dr. med. Gerhard Leyendecker.

COX-2, cyclooxygenase-2; PGE2, prostaglandin E2; OT, oxytocin; ERalpha, estrogen receptor alpha

Epidemiology

The estimated prevalence of endometriosis is 5% to 15%.

Etiology

The concept of tissue injury and repair explains how women can develop endometriosis.

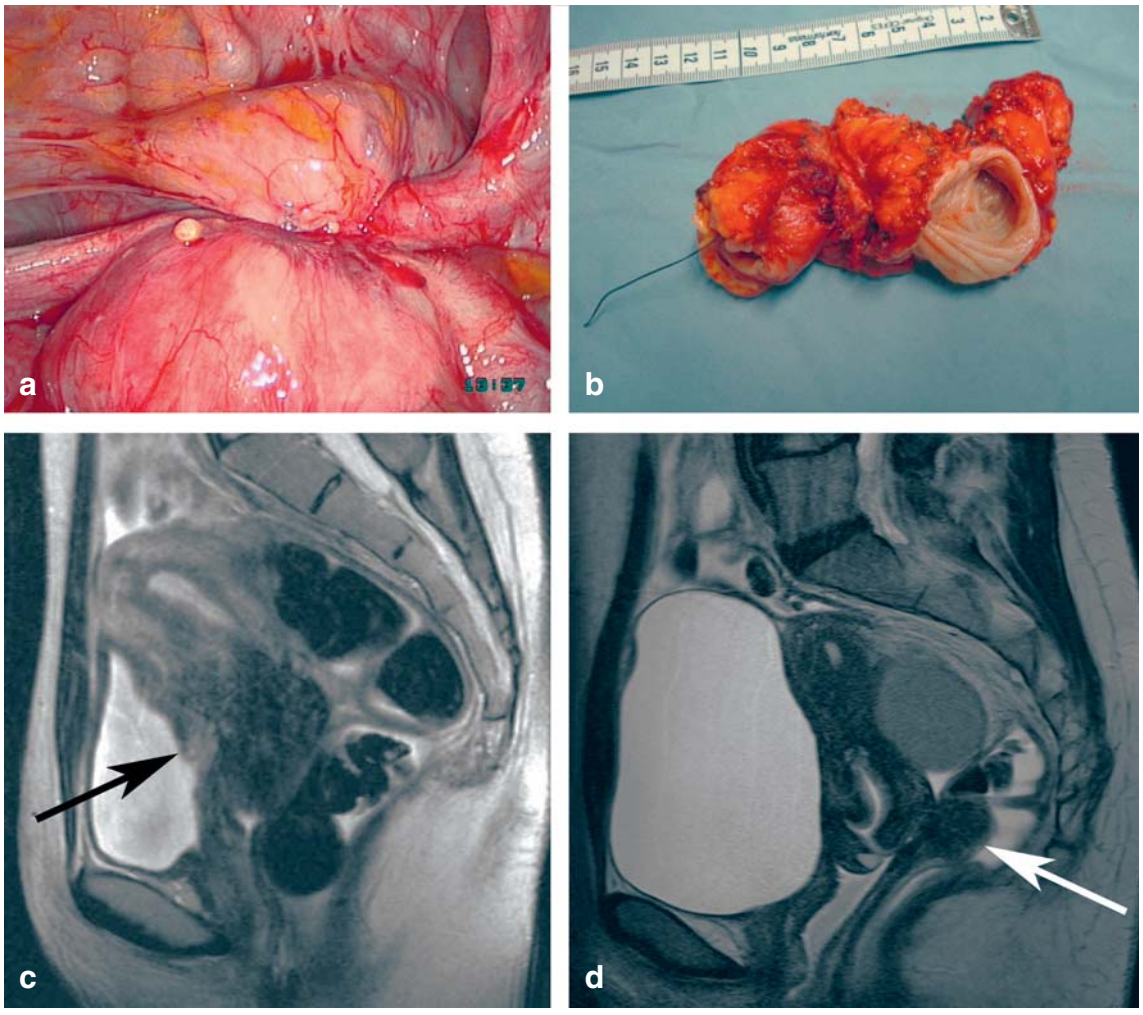


Figure 2
Typical varieties of deep infiltrating endometriosis:
a) Bladder infiltration with involvement of both round ligaments
b) Stenosing endometriosis of the rectum
c) When infiltrating endometriosis of the bladder is suspected, it is advisable to obtain an MRI scan while the patient's bladder is full, as was done here. Extensive adenomyosis of the anterior uterine wall is easily seen and also involves the transition zone between the cervix and the body of the uterus (the cervicoisthmic transition zone) (arrow)
d) MRI is the imaging method of choice for uterine adenomyosis and deep infiltrating endometriosis in the area of the rectum (arrow)

genomics and proteinomics are shedding new light on the molecular biology of endometriosis (13).

History

The main manifestations of endometriosis include:

- Pain:
  - Dysmenorrhea, which can be either primary or secondary. Primary dysmenorrhea generally begins shortly after the menarche, and it usually persists until the menopause in affected women. Some scientists, therefore, consider primary dysmenorrhea to be an early manifestation, rather than a sequela, of endometriosis. Secondary dysmenorrhea can be caused by organic diseases of various types, including endometriosis.
  - Position-dependent or -independent dyspareunia (with or without loss of libido)
  - Dyschezia
  - Pelvic pain of both cyclic and acyclic chronic types *(eBox)*
- Uterine hemorrhagic disturbances
- Primary or secondary sterility.

Women with endometriosis also complain, depending on the site of the disease, of gastrointestinal,

Major manifestations of endometriosis

- Pain accompanying or associated with menstruation, sexual intercourse, or defecation; pelvic pain
- Hemorrhagic disturbances of the uterus
- Sterility

Types of endometriosis

- Endometriosis of the bladder
- Endometriosis of the ureter
- Rectovaginal endometriosis

urological, autonomic, and nonspecific manifestations, and of symptoms resembling chronic fatigue. We have noted depressive mood alterations and/or clinically relevant depression or anxiety disorders in more than 60% of the women with endometriosis whom we have treated. Thus, whenever advanced endometriosis is diagnosed, psychotherapy should always be considered as a potential component of treatment.

Endometriosis of the bladder

Tough, nodular adenomyofibrohyperplasia is found at the site of infiltration *(Figure 2a)* and can lead to painful, ineffective bladder contractions, as well as to microcirculatory disturbances in the urothelium, with resulting micro- or macrohematuria. The diagnostic assessment includes history-taking, vaginal palpation, vaginal ultrasonography with a full bladder, and magnetic resonance imaging (MRI) *(Figure 2c)*. Invasive diagnostic techniques include cystoscopy and laparoscopy (10, 14) *(eBox)*. Transurethral resection (TUR) is contraindicated in endometriosis, because endometriosis infiltrates transmurally from the outside in, i.e., toward the endothelium, and thus cannot be removed through the urethra *(eFigure 1 a–f)*. Intravesical lesions can be biopsied through the cystoscope, and ureter stents can be inserted cystoscopically if necessary (10, 15).

Ureteric endometriosis

Endometriosis of the ureter can be either intrinsic or extrinsic (15). These two types often cannot be reliably distinguished from each other before surgery. In the external type, which is more common, the ureter is compressed by the shrinkage of endometriosis tissue that encompasses it on the outside; this finding is typically described in cases of bilateral ovarian endometriosis ("kissing ovaries," as named by Michel Mueller of Bern). The site of least resistance is the point where the sacrouterine ligament, the ureter, and the uterine artery cross (16) *(eFigure 2)*. Intrinsic ureteric endometriosis is rarer and infiltrates multiple layers of the ureter. It is present in less than 0.3% of all women with endometriosis (17). Its manifestations range from nonspecific pelvic pain to flank pain, renal obstruction (usually unilateral), and asymptomatic hydronephrosis, with loss of function of the affected kidney(s). Recommended studies for diagnostic evaluation include renal ultrasonography, an intravenous urogram, or MRI excretion urography, if available. Renal function should be assessed with laboratory tests (creatinine, blood urea nitrogen) and/or renal scintigraphy (*eBox*).

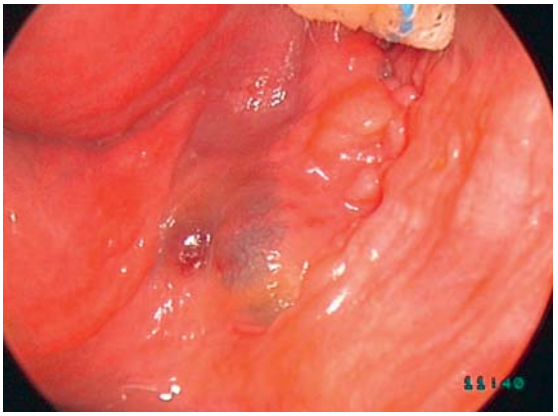


Figure 3
Typical infiltration of the posterior vaginal fornix. Such findings can be seen only if the cervix is correctly positioned with the speculum during the gynecological examination

Rectovaginal endometriosis

Rectovaginal endometriosis is usually easy to see in the posterior vaginal fornix, and easy to palpate in the rectovaginal septum *(Figure 3)*.

Infiltration of the adjacent intestine and of the sacrouterine ligaments, in addition to adhesion formation, can lead to partial or complete obliteration of Douglas's pouch. This, combined with severe accompanying adenomyosis, causes infertility. Pelvic pain is often severe; intestinal manifestations are almost always present; and dyspareunia, sometimes leading to loss of libido, is typical. These problems are due to the location of the invasive foci and their innervation (18). In endometriosis of the bowel, transmural infiltration generally leads to stenosis or, rarely, occlusion of the intestinal lumen *(Figure 2b)*. Abnormal microcirculation between the endometriosis nodule and the intestinal mucosa (less commonly, infiltration of the mucosa) causes cycle-dependent intestinal hemorrhage. Simultaneous infiltration of the parametria often involves the ureters as well (15, 19), so that bilateral ureterolysis and surgical exposure of the ureters may be necessary (9, 16, 19). For optimally precise preoperative diagnostic evaluation, history-taking and rectovaginal gynecological examination should be supplemented by transrectal ultrasonography, in combination with rectosigmoidoscopy, to determine whether the mucosa is involved. Invasive foci can be documented by MRI, which can also provide very clear evidence of

Endometriosis of the bladder

Women in whom bladder endometriosis or any other type of deep infiltrating endometriosis is suspected should undergo bilateral renal ultrasonography.

Endometriosis of the ureter

This disorder can be either extrinsic or (rarely) intrinsic. In the extrinsic form, endometriosis tissue surrounds the ureter and, when it shrinks, compresses the ureter from outside.

TABLE 1

The spectrum of efficacy of different gestagen drugs in the treatment of endometriosis*[1/2]

Gestagen	Partial effects						
	Gestagenic effect	Anti-estrogenic effect	Estrogenic effect	Anti-androgenic effect	Androgenic-anabolic effect	Gluco-corticoid effect	Anti-mineralo-corticoid effect
Progesterone derivatives							
Progesterone	+	+	–	(+)	–	(+)	+
Medroxyprogesterone acetate	+	+	–	–	(+)	+	–
Megestrol acetate	+	+	–	(+)	(+)	+	–
Chlormadinone acetate	+	+	–	+	–	+	–
Cyproterone acetate	+	+	–	+	–	+	–
Drospirenone	+	–	–	+	–	–	+
Dydrogesterone	+	+	–	(+)	–	–	(+)
Nortestosterone derivatives							
Norethisterone	+	+	+	–	+	–	–
Norethisterone acetate	+	+	+	–	+	–	–
Ethynodiol diacetate	+	+	+	–	+	–	–
Lynestrenol	+	+	+	–	+	–	–
Levonorgestrel	+	+	–	–	+	–	–
Desogestrel	+	+	–	–	+	–	–
Gestodene	+	+	–	–	+	(+)	+
Norgestimate	+	+	–	–	+	–	–
Dienogest	+	–/+	–	+	–	–	–

*[1] On the basis of recent clinical trials, dienogest (2 mg) has recently been approved in Europe for the treatment of endometriosis. Thus, alongside GnRH analogues, which are the current gold standard of treatment, a further, effective gestagen preparation has been available since May 2010 for on-label use in Germany.

*[2] Modified from e1–e3

uterine adenomyosis *(Figure 2d)*. Tissue is obtained for histological diagnosis and staging either by laparoscopy or by laparotomy. Laparotomy is now performed less commonly than in the past *(eBox)*.

The surgical treatment of endometriosis

General principles

Endometriosis is a chronic, hormone-dependent disease of the uterus, with a highly variable clinical course. Thus, the treatment should be designed according to the patient's individual needs. This does not mean that it should be chosen arbitrarily (20). The physician should discuss with the patient whether the primary reason for treatment is acute or chronic endometriosis-related pain or an as yet unfulfilled desire to bear children (21).

The biology of endometriosis implies that the best way to treat symptomatic patients is with an individualized combination of surgery and endocrine (usually anti-estrogenic) pharmacotherapy, supported by complementary treatment approaches *(eTable 1)*.

Laparoscopy is the gold standard for the surgical treatment of endometriosis. Robust evidence is currently unavailable for the surgical methods that are used to treat endometriosis or deep infiltrating endometriosis (as is the case for many other diseases as well).

Rectovaginal endometriosis

In most cases, this type of endometriosis is readily seen in the posterior vaginal fornix and in the rectovaginal septum.

Renal ultrasonography

In rectovaginal endometriosis, both kidneys should always be ultrasonographically examined. In women with renal obstruction, cervical carcinoma *and* endometriosis should always be ruled out.

TABLE 2

Recommendations for endocrine pharmacotherapy of endometriosis*[1]

Substance	Dosage
GnRH analogues (selected)	
Leuporelin acetate	3.75 mg / 4 weeks SC
Leuporelin acetate	Three-month depot SC
Goserelin acetate	3.8 mg / 4 weeks SC
Buserelin acetate	3–4 × 300 µg/d
Nafarelin acetate	2–4 × 460 µg/d
Triptorelin acetate	105 µg/d
Parenteral gestagen preparataions (selected)	
Medroxyprogesterone acetate	150 or 104 mg IM every 12 weeks
Etonogestrel	68 mg SC implant for up to three years
Norelgestromin	One patch per week
Gestagen-containing intrauterine devices	
Levonorgestrel	20 µg / 24 h
Progesterone derivatives (selected)	
Medroxyprogesterone acetate (MPA)	30–50 mg/d
Medrogestone	50–75 mg/d
Nortestosterone derivatives (selected)	
Lynestrenol	10 mg/d
Desogestrel	0.075–0.15 mg (= 1–2 Tabl/d)
Dienogest*[2]	2 mg/d
Combined oral contraceptives (selected)	
Second-generation preparations	
Levonorgestrel	100 µg + 20 µg EE
Levonorgestrel	150 µg + 30 µg EE
Levonorgestrel	250 µg + 30 µg EE
Norethisterone	0.5 mg + 20 µg EE
Norethisterone acetate	0.5 mg + 30 µg EE
Norethisterone acetate	1.5 mg + 30 µg EE
Third-generation preparations	
Dienogest *[2]	2 mg + 30 µg EE
Norgestimate	250 µg + 35 µg EE
Gestodene	0.750 µg + 30 µg EE
Desogestrel	150 µg + 20 µg EE
Desogestrel	150 µg + 30 µg EE
Chlormadinone acetate	2 mg + 30 µg EE

*[1] The oral contraceptives that are currently available in Germany contain the following gestagens: desogestrel, norethisterone, levonorgestrel, drospirenone, chlormadinone acetate, gestodene, dienogest, norgestimate, lynestrenol.
The non-oral contraceptives contain the following gestagens: etonogestrel, medroxyprogesterone acetate, norelgestromin, levonogestrel (also see *Table 1*)

*[2] No off-label use. Currently not an oral contraceptive agent. Dienogest could also be categorized as a progesterone derivative

EE, ethinyl estradiol

Endocrine pharmacotherapy

In general, once the diagnosis of endometriosis has been histologically confirmed, hormonal drugs are used for neoadjuvant and adjuvant treatment and in cases of recurrence.

Potential side effects of the gestagens used to treat endometriosis:

Breakthrough bleeding, weight gain, fluid retention, skin changes, heat waves, breast tenderness, headache, vaginal dryness

Although the best treatment for endometriosis is generally surgery combined with pharmacotherapy, asymptomatic patients with stenosing ureteric endometriosis are an exception to this rule. For these patients, surgical treatment is clearly indicated (evidence level 1a). It remains unclear whether asymptomatic ovarian endometriomas require operative treatment, and surgery in this area can damage the adjacent normal ovarian tissue. The question is relevant for no more than a few women, as only about 5% to 10% of all cases of endometriosis are thought to be asymptomatic (evidence level 4). At any rate, it is just as wrong to neglect the clinical manifestations of endometriosis *(eBox)* as it is to pursue zealous medical and/or surgical overtreatment of the disease, while disregarding the psychosomatic, social, occupational, and conjugal problems that it causes. Cyclical symptoms and pain that make a woman feel ill, confine her to bed, or lead her to abuse medications require timely clinical and laparoscopic evaluation by a gynecologist. Endometriosis should be either excluded or confirmed before any treatment is initiated. The most serious complication of endometriosis treatment is chronification of the patient's symptoms.

Endometriosis of the bladder

The primary treatment modality for symptomatic endometriosis of the bladder is surgery (10, 15). The surgeon's experience determines whether this is best done via laparoscopy or laparotomy (10, 14). A number of innovative surgical techniques have been developed (10, 15, 17).

First, the infiltrated portion of the bladder should be dissected free of the body of the uterus or the cervicoisthmic junction until the macroscopically disease-free vesico-uterine space is reached *(eFigure 1)*. Next, a whetstone- or orange-slice-shaped partial vesical resection is performed (10). The trigone of the bladder near the ostium, together with its neural structures, is the most vulnerable part of the bladder whenever partial vesical resection is performed, either openly or laparoscopically (10, 15). Nonetheless, an R0 resection should be the goal. The bladder is then closed with a seromuscular suture and tested for leak tightness by retrograde filling with methylene blue dye. Transurethral urinary drainage is recommended for six days after surgery. The most serious complication of this operation is a so-called neurogenic bladder: vesical denervation, caused either by endometriosis or its treatment, may necessitate either permanent catheterization or the implantation of a vesical neurostimulator in a young female patient. Adjuvant anti-endocrine therapy is given in accordance with the current national guidelines for deep infiltrating endometriosis (e4).

Rehabilitation measures or treatment in specialized facilities is indicated for many women who suffer from endometriosis as a chronic disease (evidence level 4).

Endometriosis of the ureter

Surgery for deep infiltrating endometriosis, or for pelvic adhesions secondary to endometriosis, carries an elevated risk of ureteric complications (9). These can include urinoma formation or uroperitoneum leading to infection or other adverse consequences for the involved kidney. Complex operations should be planned and carried out in an interdisciplinary collaboration (20). In extrinsic ureteric endometriosis, the goal of surgery is freeing (ureterolysis) and decompression of the ureter (15). In intrinsic ureteric endometriosis, an additional objective is partial resection of the ureter with end-to-end anastomosis or direct ureteric neoimplantation, e.g., with the psoas hitch technique (15). The ureter often must be freed of surrounding tissue all the way to its junction with the bladder to allow safe resection of the infiltrated parametria. At the same time, the retroperitoneal course of nerves lying in the operative field (such as the hypogastric, splanchnic, femoral, and obturator nerves) must be laparoscopically exposed, so that a neurogenic bladder-emptying disturbance can be avoided. After extensive surgery in the area of the ureters, it is recommended that ureteric stents should be left in place for four to six weeks.

Rectovaginal endometriosis

Asymptomatic or oligosymptomatic deep infiltrating endometriosis is rare and can be treated conservatively, after thorough discussion with the patient, as long as evaluation reveals no stenosis, hemorrhage, or progressive disease needing treatment. Such patients should undergo annual rectovaginal examinations by an experienced gynecologist. Depending on the findings, further diagnostic studies may be indicated, e.g., MRI of the uterus and rectovaginal septum or transrectal ultrasonography, combined with rectosigmoidoscopy where appropriate (evidence level 2). Surgery is currently the treatment of choice for symptomatic rectovaginal endometriosis (20). Many operative techniques

Symptomatic rectovaginal endometriosis

Surgery is currently the method of choice for treating this disorder.

The treatment of choice

Laparoscopy is the gold standard for the surgical treatment of endometriosis. Robust evidence is currently unavailable for the surgical methods used to treat deep infiltrating endometriosis.

have been developed for this purpose, all of them with the goal of an R0 resection *(eTable 1)*. Regardless of the surgical approach used, the infiltrated rectosigma or sigma must be mobilized away from normal and pathological adhesions *(Case Illustration)* and then resected, after which an end-to-end anastomosis is performed. The patient must, of course, be fully informed about the nature of the procedure before it is performed (16, 19). Women with deep infiltrating endometriosis are today best served by treatment in a specialized endometriosis center. This is the case because of the potential complications of treatment, which become more likely with increasing severity of the illness. Special attention must be paid to the problem of suture-line dehiscence leading to rectovaginal fistula formation and further problems (22–24). As far as the treatment of pain is concerned, the data from clinical trials published to date have not led to the widespread adoption of laparoscopic uterine nerve ablation (LUNA) or other nerve-ablation techniques. Any adjuvant and/or experimental treatments that might be proposed should be discussed with the patient individually, in the light of her particular clinical circumstances and living situation (25).

Endocrine treatment

Once the diagnosis of endometriosis is histologically confirmed, endocrine pharmacotherapy can be used as a neo-adjuvant or adjuvant measure, as well as for the treatment of recurrences. Surgeons generally do not favor neo-adjuvant endocrine pharmacotherapy because of its unfavorable effect on tissue planes. In cases of extensive endometriosis, and particularly in deep infiltrating endometriosis, an R0 resection can only rarely be achieved. It therefore makes sense to give adjuvant endocrine pharmacotherapy with the goal of transient therapeutic amenorrhea. The following options are available at present:

a) gestagens
b) oral contraceptives
c) GnRH analogues
d) pain therapy
e) combinations of the above
f) experimental treatment approaches.

Gestagens

Gestagens effect a secretory transformation of the endometrium after previous exposure to estrogens *(Tables 1 and 2)*.

The potential side effects of gestagen supplementation are:

- breakthrough bleeding (40% to 80%)
- weight gain and fluid retention (40% to 50%)
- acne, skin changes of endocrine origin, and other skin problems (20%)
- hot flashes, loss of libido (more than 30%)
- breast tenderness (10%)
- headache (10%)
- vaginal dryness, transient alopecia, osteopenia, mood swings (10%)

Gestagens also have an effect on a variety of metabolic processes and indices:

- atherogenic indices (rising LDL, falling HDL)
- carbohydrate metabolism (lower glucose tolerance, rising insulin resistance).

Gestagen supplementation has also been found to lead to a higher incidence of venous thromboembolism. Other long-term effects include a mild natriuretic effect, alteration of cervical secretions, and vaginal candidiasis (a common finding).

Oral contraceptives

Oral contraceptives (when used off label for this indication) bring about a so-called pseudopregnancy regimen *(Table 2, eTable 1)*. Their well-known side effects, which vary in frequency from one preparation to another, include breakthrough bleeding, nausea, headache, and an elevated risk of venous thromboembolism, as well as loss of libido, cutaneous reactions, sodium and fluid retention leading to weight gain, breast tenderness, and a rise in blood pressure. Generally, however, oral contraceptives are very well tolerated.

The goal of treatment is suppression of the menses (therapeutic amenorrhea). If breakthrough bleeding occurs, the patient can take one oral contraceptive tablet twice a day for as long as smear bleeding persists and for one day afterward, and then return to a single tablet per day. It is important for the patient to be properly informed.

GnRH analogues

GnRH analogues bring about a "functional oophorectomy," i.e., a state of pharmacologically induced hypogonadotropic hypogonadism (Table 2, eTable 1). This, in turn, causes well-recognized side effects:

- hot flashes and perspiration (80% to 90%)
- sleep disturbance (60% to 90%)
- vaginal dryness (30%)

Options for pharmacotherapy

- Gestagens
- Oral contraceptive drugs
- GnRH analogues
- Analgesics

Women with endometriosis who want to have children

The treatment of women who want to become pregnant and bear children should not involve hormonal drugs, as these do not improve fertility.

- headache (20% to 30%)
- mood changes (depressive mood change because of estrogen withdrawal, more than 10%)
- osteopenia, loss of libido (more than 30%)
- weight gain (ca. 15%).

Combined treatment approaches (pharmacotherapy and pain therapy)

In addition to surgery and pharmacotherapy, complementary treatments can be used whose efficacy has not been documented by scientific evidence. Women whose quality of life is impaired by cyclical or chronic pain want treatment in order to achieve a pain-free state with a better quality of life and an improved ability to engage in productive activities *(eTable 2)*. In a specialized endometriosis center, the patient's individual situation can be stabilized or improved through a team effort, with the active participation of the patient herself, her treating gynecologist, the surgeon, the pain specialist, and the psychotherapist. Before treatment, these women's problems are often severe enough to cause the loss of a job or of a life partner.

Experimental treatment approaches

Endometriosis cells manifest properties such as invasiveness, migration, metastasis, angiogenesis, and neurogenesis that call to mind similar properties of malignant tumors. Their responsiveness to cytokines, tumor necrosis factor (TNF-α), cyclooxygenase-2 (COX-2), oxytocin, and aromatase is currently being exploited in the attempt to devise new methods for diagnosis and treatment (3, 4, 13, 25). Although a combination of aromatase inhibitors with gestagens or GnRH analogues has been proven effective, the practicality of this form of treatment is currently limited both by its side effects and by its cost (4).

Overview

Therapeutic nihilism is not justified, even for women with extensive endometriosis. Germany is currently in the European vanguard with respect to the quality of care for patients with endometriosis, the available institutional structures for patient care and research, physician training, continuing medical education, and the certification of endometriosis centers at various levels. All of these activities are carried out with the aid of the German Foundation for Endometriosis Research (Stiftung Endometriose-Forschung [SEF]), the European Endometriosis League (EEL), and the German Endometriosis Association (Endometriose-Vereinigung Deutschland e.V.) (an umbrella organization of self-help groups).

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Conflict of Interest Statement

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REFERENCES

1. Meyer R: Die Pathologie der Bindegewebe, Geschwülste und der Mischgeschwülste. In: Stoeckel W (ed.): Handbuch der Gynäkologie. München: J.F. Bergmann1930, 211–853.
2. Leyendecker G, Herbertz M, Kunz G, Mall G: Endometriosis results from the dislocation of basal endometrium. Hum Reprod. 2002; 17: 2725–36.
3. Mechsner S, Bartley J, Loddenkemper C, Salomon DS, Starzinski-Powitz A, Ebert AD: Oxytocin receptor expression in smooth muscle cells of peritoneal endometriotic lesions and ovarian endometriotic cysts. Fertil Steril. 2005; 83 (Suppl 1): 1220–31.
4. Bulun SE: Endometriosis. N Engl J Med 2009; 360: 268–79.
5. Mechsner S, Schwarz J, Thode J, Loddenkemper C, Salomon DS, Ebert AD: Growth-associated protein 43-positive sensory nerve fibers accompanied by immature vessels are located in or near peritoneal endometriotic lesions. Fertil Steril 2007; 88: 581–7.
6. Leyendecker G, Kunz G, Noe M, Herbertz M, Mall G. Endometriosis: a dys-function and disease of the archimetra. Hum Reprod Update 1998; 4: 752–62.
7. Leyendecker G, Wildt L, Mall G: The pathophysiology of endometriosis and adenomyosis: tissue injury and repair. Arch Gynecol Obstet 2009; 280: 529–38.
8. Ebert AD, Fuhr N, David M, Schneppel L, Papadopoulos T: Histological confirmation of endometriosis in a 9-year-old girl suffering from unexplained cyclic pelvic pain since her eighth year of life. Gynecol Obstet Invest 2009; 67: 158–61.
9. Donnez J, Jadoul P, Donnez O, Squifflet J: Laparoscopic excision of rectovaginal and retrocervical endometriotic lesions. In: Donnez J (ed.) Atlas of operative laparoscopy and hysteroscopy. Informa UK Ltd. 2007; 63–75.

Experimental approaches

New approaches to the diagnosis and treatment of endometriosis involve cytokines, tumor necrosis factor, cyclooxygenases, oxytocin, and aromatases.

Complementary treatment approaches

As discussed in the text, these can be used in addition to pharmacotherapy and surgery.

10. Donnez J, Squifflet J, Donnez O, Jadoul P: Bladder endometriosis. In: Donnez J (ed.) Atlas of operative laparoscopy and hysteroscopy. Informa UK Ltd. 2007; 85–91.
11. Clement PB: History of gynecological pathology. IX. Dr. John Albertson Sampson. 1921. Int J Gynecol Pathol 2001; 20: 86–101.
12. Forte A, Schettino MT, Finicelli M, et al.: Expression pattern of stemness-related genes in human endometrial and endometriotic tissues. Mol Med 2009; 15: 392–401.
13. Ferrero S, Gillott DJ, Remorgida V, Ragni N, Venturini PL, Grudzinskas JG: Proteomics technologies in endometriosis. Expert Rev Proteomics 2008; 5: 705–14.
14. Granese R, Candiani M, Perino A, Venezia R, Cucinella G: Bladder endometriosis: laparoscopic treatment and follow-up. Eur J Obstet Gynecol Reprod Biol 2008; 140: 114–7.
15. Pérez-Utrilla Pérez M, Aguilera Bazán A, Alonso Dorrego JM, et al.: Urinary tract endometriosis: clinical, diagnostic, and therapeutic aspects. Urology 2009; 73: 47–51.
16. Schonman R, De Cicco C, Corona R, Soriano D, Koninckx PR: Accident analysis: factors contributing to a ureteric injury during deep endometriosis surgery. BJOG 2008; 115: 1611–5.
17. Seracchioli R, Mabrouk M, Montanari G, Manuzzi L, Concetti S, Venturoli S: Conservative laparoscopic management of urinary tract endometriosis (UTE): surgical outcome and long-term follow-up. Fertil Steril. 2009 May 28. [Epub ahead of print].
18. Wang G, Tokushige N, Russell P, Dubinovsky S, Markham R, Fraser IS: Hyperinnervation in intestinal deep infiltrating endometriosis. J Minim Invasive Gynecol 2009; 16: 713–9.
19. Slack A, Child T, Lindsey I et al.: Urological and colorectal complications following surgery for rectovaginal endometriosis. BJOG 2007; 114: 1278–82.
20. Vercellini P, Carmignani L, Rubino T, Barbara G, Abbiati A, Fedele L: Surgery for Deep Endometriosis: A Pathogenesis-Oriented Approach. Gynecol Obstet Invest 2009; 68: 88–103.
21. Marcoux S, Maheux R, Bérubé S: Laparoscopic surgery in infertile women with minimal or mild endometriosis. Canadian Collaborative Group on Endometriosis. N Engl J Med 1997; 337: 217–22.
22. D'Hooghe T, Hummelshoj L: Multi-disciplinary centres/networks of excellence for endometriosis management and research: a proposal. Hum Reprod 2006; 21: 2743–8.
23. Ebert AD, Jakisch D, Müller MD et al.: Endometriosezentren verschiedener Stufen zur Verbesserung der medizinischen Versorgungsqualität, der Forschung sowie der ärztlichen Fort- und Weiterbildung. J Gynäkol Endokrinol 2008; 18: 62–68.
24. Beilecke K, Ebert AD: Urogenitale Endometriose. In: Tunn R, Hanzal E, Perucchini D (eds.): Urogynäkologie in Praxis und Klinik. Berlin-New York 2010: 353–73.
25. Ozkan S, Arici A: Advances in treatment options of endometriosis. Gynecol Obstet Invest. 2009;67:81–91.

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This article has been certified by the North Rhine Academy for Postgraduate and Continuing Medical Education.

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The CME unit "Decubitus Ulcers: Pathophysiology and Primary Prevention" (issue 21/2010) can be accessed until 9 July 2010.

For issue 28–29/2010 we plan to offer the topic "The Treatment of HIV Patients."

Solutions to the CME questionnaire in issue 17/2010:
Jahn, Klaus, et al.: "Gait Disturbances in Old Age: Classification, Diagnosis, and Treatment from a Neurological Perspective."
Answers: 1c, 2d, 3e, 4a, 5c, 6e, 7a, 8d, 9d, 10a

Please answer the following questions to participate in our certified Continuing Medical Education program. Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

What is the most current hypothesis regarding the origin of endometriosis?

a) The metaplasia hypothesis
b) The transplantation hypothesis
c) The induction hypothesis
d) The tissue injury and repair hypothesis
e) The aromatase hypothesis

Question 2

Which of the following is a manifestation of endometriosis?

a) Hyperglycemia
b) Hyperbilirubinemia
c) Anemia
d) Steatorrhea
e) Dysmenorrhea

Question 3

By what criterion is endometriosis classified in the German-language literature?

a) By histology
b) By clinical manifestations
c) By site
d) By duration
e) By the age of the patient

Question 4

What is the estimated prevalence of endometriosis among all women of child-bearing age?

a) 5–15%
b) 25–35%
c) 45–55%
d) 65–75%
e) 85–95%

Question 5

What is the imaging technique of first choice for the differential diagnosis of uterine adenomyosis and deep infiltrating endometriosis?

a) Plain x-ray
b) Ultrasound
c) Doppler ultrasonography
d) Magnetic resonance imaging
e) Computerized tomography

Question 6

What test should be performed in all women in whom there is a well-founded clinical suspicion of endometriosis of the bladder or any other type of deep infiltrating endometriosis?

a) Cystoscopy
b) Colonoscopy
c) Renal ultrasonography
d) Vaginal swab
e) pH measurement of vaginal flora

Question 7

What is the definition of extrinsic endometriosis of the ureter?

a) Expansion of endometriosis tissue within the ureter, creating pressure on the ureter from within
b) Compression of the ureter from outside by shrinking endometriosis tissue that surrounds the ureter
c) Infiltration of ureteric tissue by assimilation of external endometriosis tissue
d) The presence of endometriosis tissue outside the uterus
e) Perforation of the uterus by endometriosis tissue located outside it

Question 8

What progesterone derivative used in the treatment of endometriosis is characterized by a positive gestagenic effect, a negative anti-estrogenic effect, and a negative estrogenic effect?

a) Progesterone
b) Cyproterone acetate
c) Chlomadinone acetate
d) Drospirenone
e) Dydrogesterone

Question 9

What group of patients should undergo immediate surgery without concomitant pharmacotherapy?

a) Asymptomatic patients with deep infiltrating peritoneal endometriosis
b) Asymptomatic patients with stenosing ureteric endometriosis
c) Symptomatic patients with deep infiltrating ovarian endometriosis
d) Symptomatic patients with deep infiltrating ureteric endometriosis
e) Asymptomatic patients with deep infiltrating vesical endometriosis

Question 10

What is the definition of endometriosis?

a) A disease of the uterus in which tissue from the uterine cavity becomes implanted in the abdominal cavity
b) A disease of the uterus in which tissue from the pelvic cavity becomes implanted in the abdominal cavity
c) A disease in which tissue from the peritoneal cavity becomes implanted in the abdominal cavity
d) A disease in which tissue from the intra-abdominal space becomes implanted in the abdominal cavity
e) A disease in which vaginal epithelium becomes implanted in the abdominal cavity

CONTINUING MEDICAL EDUCATION

The Diagnosis and Treatment of Deep Infiltrating Endometriosis

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eReferences

e1. Göretzlehner G, Lauritzen C, Göäretzlhener U: Praktische Hormontherapie in der Gynäkologie. 5. Auflage Berlin: de Gruyter 2007.

e2. Teichmann AT: Kontrazeption – ein Kompendium für Klinik und Praxis Stuttgart: Wissenschaftliche Verlagsgesellschaft 1991.

e3. Kuhl C, Jung-Hoffmann C: Kontrazeption. Stuttgart: Thieme 1996.

e4. Ulrich U: Leitlinien Diagnostik und Therapie der Endometriose AWMF 2010. www.uni-duesseldorf.de/AWMF/ll/015–045.htm

eBox

The minimum required diagnostic evaluation when deep infiltrating endometriosis is suspected*[1]

History-taking gives the physician the opportunity to become thoroughly acquainted with the patient and her complaints and to correlate the symptoms with the physical findings.

- Historical aspects
  - Always pay attention to the dynamics and temporal course of the patient's symptoms
  - When was the first menstrual period? Was the first period already painful? Did the patient have to miss school because of painful menstruation? Did painful menstruation lead to excessive use of analgesics or to the administration of oral contraceptives?
  - How long have the symptoms been present? Have they changed over time, and if so, how?
  - Endometriosis-associated complaints can be cyclical, acyclical, or chronic.
  - What previous operations have been performed, by whom, when, where, and with what result? Can operative notes from the previous operations be obtained?
  - What endocrine treatments have been carried out to date, from when until when, and with what result?
  - From when until when were other forms or treatment tried (acupuncture, TCM, naturopathy, homeopathy), and with what result?
  - Dysmenorrhea: primary? Secondary?
  - Dyspareunia: position-dependent? Position-independent? Loss of libido? Conjugal problems? Psychogenic dyspareunia?
  - Abnormal bleeding: abnormalities of menstrual rhythm? Abnormalities of the type of menstrual bleeding? Hypermenorrhea? Additional bleeding?
  - Pelvic pain: cycle-dependent? Cycle-independent? Chronic? Perimenstrual back pain?
  - Urogenital symptoms: Dysuria? Polyuria? Pollakisuria? "Irritable bladder"? Frequent bouts of cystitis? Microhematuria? Macrohematuria? Perimenstrual incontinence? Urinary obstruction? "Interstitial cystitis"?
  - Gastrointestinal symptoms: constipation, pseudodiarrhea, postprandial cramps, hematochezia, dyschezia, "irritable bowel," perimenstrual tenesmus and painful bloating, perimenstrual change of stool consistency?
  - Psychosomatic and psychiatric abnormalities: fatigue? Depressive symptoms/disturbances? Anxiety disturbances? Medication abuse? Social status? Social problems? Conjugal problems?
  - Previous surgery: adnexal surgery? Endometriosis surgery? Other?
  - Previous illnesses: Diabetes? Hypertension? Depression? Thyroid? Other?
  - Previous treatments: infertility treatment? Psychiatric treatment? Treatment of thyroid disorders? Other?
  - Medication use: oral contraceptives? GnRH analogues? Gestagens? Other (e.g., antidiabetic agents, antidepressants)?
- Gynecological examination
  - Speculum position—always remember to inspect the anterior and posterior vaginal fornices for macroscopic exclusion of infiltration that has already taken place!
  - Inspection, colposcopy when indicated. When typical findings are seen in the vagina, vaginal biopsy under local anesthesia may be useful.
  - Always perform rectovaginal palpation (under general anesthesia if the patient is undergoing a procedure)
- Ultrasonography
  - Transvaginal ultrasonography: ovarian endometriomas? Uterine adenomyosis? Bowel involvement?
  - Abdominal ultrasonography: renal ultrasonography and ultrasonography with a full bladder for the evaluation of possible vesical endometriosis
  - Transanal ultrasonography: endosonography combined with rectosigmoidoscopy to rule out rectal endometriosis. Bowel involvement? What layers? Probably an especially important issue with proximally located infiltration of the rectosigmoid colon, beyond the reach of the palpating finger
- Laboratory values
  - CA-125, urinalysis, bacteriology, ß-HCG when indicated, CRP. In endometriosis, the tumor marker CA125 seldom reaches values as high as those seen in ovarian carcinoma; in many cases, it rises only in the setting of active disease.
- Imaging studies and invasive diagnostic tests
  - Magnetic resonance imaging (better than CT) is the method of choice when adenomyosis or deep infiltrating endometriosis is suspected. In cases of suspected infiltration of the bladder, MRI should always be performed with a full bladder; in suspected rectal infiltration, contrast-enhanced rectal MRI yields very clear findings.
  - Intravenous urography (if ureteric involvement is suspected)
  - Cystoscopy, combined with biopsy if indicated (e.g., to rule out interstitial cystitis), but never perform a transurethral resection to treat vesical endometriosis
  - Rectosigmoidoscopy should be performed at the time of the menses if possible; (surgical) laparoscopy with histological confirmation of the diagnosis and staging of disease is the gold standard for diagnostic evaluation. There is no such thing as "diagnostic laparoscopy" for endometriosis; laparoscopy is always a surgical procedure.
  - In case of cyclical hemoptysis, perform a spiral CT of the chest to rule out pulmonary endometriosis (an extremely rare entity).

*[1]There are no current guideline recommendations for the diagnostic evaluation of endometriosis. The fact that no recommendation *for* a particular method can be given should not be interpreted as a recommendation *against* it.

eTABLE 1

Current treatments of endometriosis (modified from [24])

Treatment	Remarks	
Surgical treatments The current gold standard of surgical treatment is laparoscopy. It nonetheless remains true that a safe laparotomy is better than an unsafe laparoscopy, as the main risk factor in endometriosis surgery is the primary surgeon. Robust evidence is not available to support the surgical methods used to treat endometriosis and deep infiltrating endometriosis (and the same holds for many other surgically treated diseases).	Peritoneal endometriosis	Complete removal of implanted endometriosis tissue (scissors, laser, or ultrasound)
	Ovarian endometriosis	Complete, meticulous shelling-out of endometriomas. The surrounding healthy tissue must be preserved, and seeding of viable endometriosis cells through iatrogenic cyst rupture must be avoided.
	Deep infiltrating endometriosis	– Laparoscopically assisted surgery – Combined transvaginal and laparoscopic surgery – Combined transvaginal-laparoscopic-open surgery – Transvaginal-laparoscopic surgery – Abdominal incision, too, in some cases
	Uterine adenomyosis	Types of hysterectomy: abdominal hysterectomy (AH), total laparoscopic hysterectomy (TLH), laparoscopic supracervical hysterectomy (LASH). LASH is not recommended because of morcellation of the uterus and the resulting intra-abdominal dispersion of tissue. Vaginal hysterectomy (VH) is not recommended by the authors because of the lack of opportunity to remove any additional foci of endometriosis that might be present. Organ-preserving techniques: – Surgical: hysteroscopic or laparoscopic resection of submucosal or transmural foci of adenomyosis (possible with organ preservation only in rare cases) – Endocrine: therapeutic induction of amenorrhea: nonstop oral contraceptives, gestagens, GnRH analogues, or (better) hormone spirals can be considered
	Sterility	Surgical removal of implanted endometriosis tissue improves the chances for spontaneous conception. Assessment of tubal patency, removal of endometriomas. If extensive endometriosis is present, assisted reproduction is necessary (IVF/ICSI)
Pharmacotherapeutic modalities	Gestagens	Antigonadotropic and anti-estrogenic effect, reduction of macrophage quantity and activity
	Combined oral contraceptives	Central inhibition of ovarian function with the goal of therapeutic amenorrhea when taken nonstop
	GnRH analogues	Ovarian suppression through effect on the hypothalamic-pituitary system; given in long or ultra-long protocols to patients with endometriosis-associated sterility
	Pain therapy	Nonsteroidal anti-inflammatory drugs (NSAID), COX inhibitors, mild opioids, antidepressants, combinations of the above
	COX-2 inhibitors, aromatase inhibitors (evidence level 1), TNF inhibitors, oxytocin inhibitors, PAARP inhibitors, etc.	Experimental approaches, causal and non-causal, mostly not studied in clinical trials
Complementary approaches and initial measures Rehabilitation or postsurgical treatment in specialized facilities is often indicated for patients suffering from endometriosis as a chronic disease (evidence level 4).	Psychosomatic therapy	Positive thinking, relaxation techniques, imagery, etc.
	Physiotherapy	Diagnosis and treatment of functional disturbances of the body
	Nutrition	Balanced diet with adequate vitamins and minerals, reduction of alcohol, sugar, and caffeine intake, exclusion of fructose or lactose intolerance
	Traditional Chinese medicine	Acupuncture, acupressure, moxibustion, herbal medicine, qi gong
	Ayurveda	Traditional Indian medicine
	Homeopathy	"Like is cured by like"
	Osteopathy	Diagnosis and treatment of functional disturbances of the body

eTABLE 2

Nonsteroidal anti-inflammatory drugs (NSAID) and coanalgesics in the pharmacotherapy of endometriosis-related pain

Substance	Recommended dose	Remarks
Diclofenac	50–150 mg/d (2–3 ×/d) or 100 mg sustained release/d	Beware of elevated risk of GI ulcers, give ulcer prophylaxis from the start of treatment (all NSAID are comparable)
Ibuprofen	200–2400 mg/d (3–4 ×/d) or Ibuprofen 800 mg sustained release (max. 3 x 800 mg/d)	Adverse effects: insomnia, asthma, alopecia, psychotic reactions, weight gain (edema formation, compatible risk for all NSAID), increased opportunity for abuse because of ready availability, watch for signs of overuse!
Naproxen	500–1000 mg/d (2–4 ×/d)	
Metamizole sodium	8–16 mg per kg body weight, up to 4 ×/d	
Etoricoxib	1 × 90–1 × 120 mg/d	Adverse effects: edema, diarrhea, and dizziness have been described. Rarely, arrhythmia and cardiovascular events; inadequate data on possible effects during pregnancy and breastfeeding. Effective against endometriosis-associated pain, but not specifically approved for endometriosis: off-label use
Celecoxib	2 × 200–400 mg/d	Idem: etoricoxib Off-label use
Coanlagesics and opioids		
Amitriptyline	12.5–75 mg/d (in the evening)	Better sleep, cholinergic side effects, checking of ECG, blood counts, and transaminases required, slow dose titration
Nortriptyline	Cf. amitriptyline	Cf. amitriptyline; less sedation and other adverse effects
Gabapentin	1800–3600 mg/d (in 3 doses)	The best-tolerated anticonvulsant drug; slow dose titration (alternative: pregabalin)
Tramadol	Individual titration; 100–200 mg sustained release (2 ×/d)	Not subject to German narcotic regulations; a weak opioid with additional, non-opioid-receptor-mediated analgesia
Tilidine/naloxone	Individual titration; from 2 × 100 to 3 × 200 mg sustained release/d	Not subject to German narcotic regulations; a weak opioid combined with an opioid antagonist (effective only in case of overdose)
Morphine sulfate	Individual titration	Sedation, dizziness, headache, respiratory depression, dry mouth, constipation, orthostatic hypotension, bradycardia; life-threatening interaction with certain types of antidepressants (MAO inhibitors) affecting CNS, respiratory, and circulatory function, do not give until at least 14 days after discontinuation of MAO inhibitor
Fentanyl	Individual titration	Transdermal system (change every three days), only for long-term use

CONTINUING MEDICAL EDUCATION

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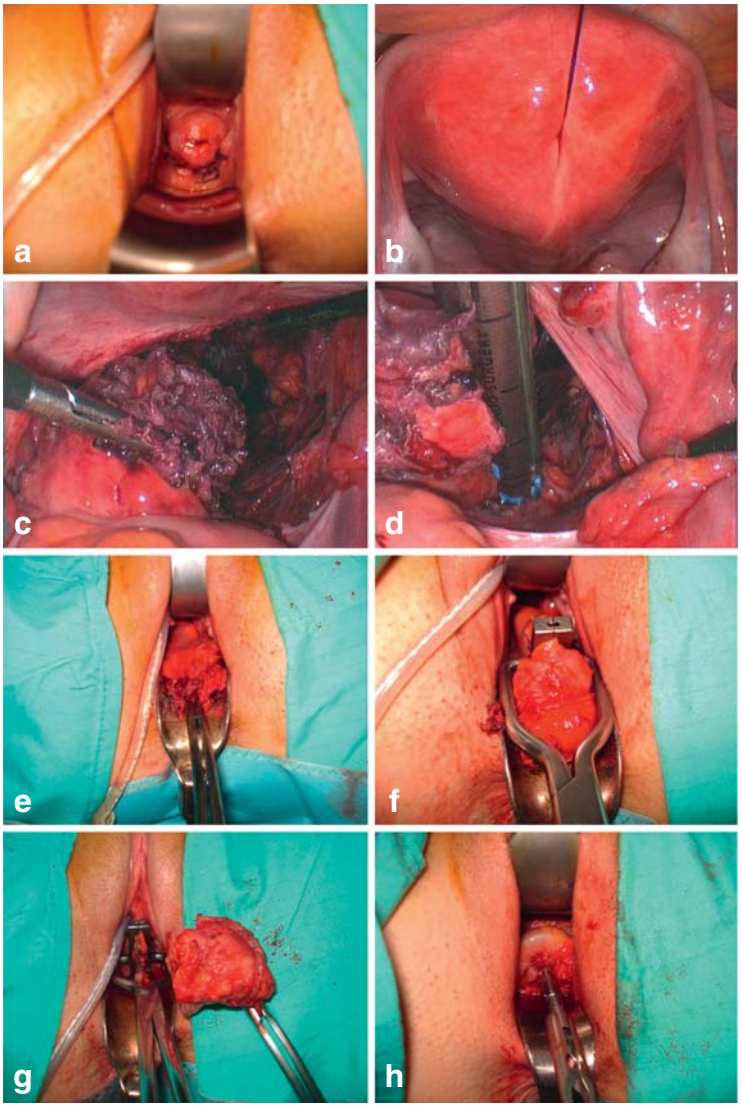


Case Illustration

A 23-year-old woman presented with severe abdominal pain and was found to have factor VII deficiency and endometriosis. A transvaginal laparoscopic anterior resection of the rectum (TLARR) was performed as the treatment of choice.

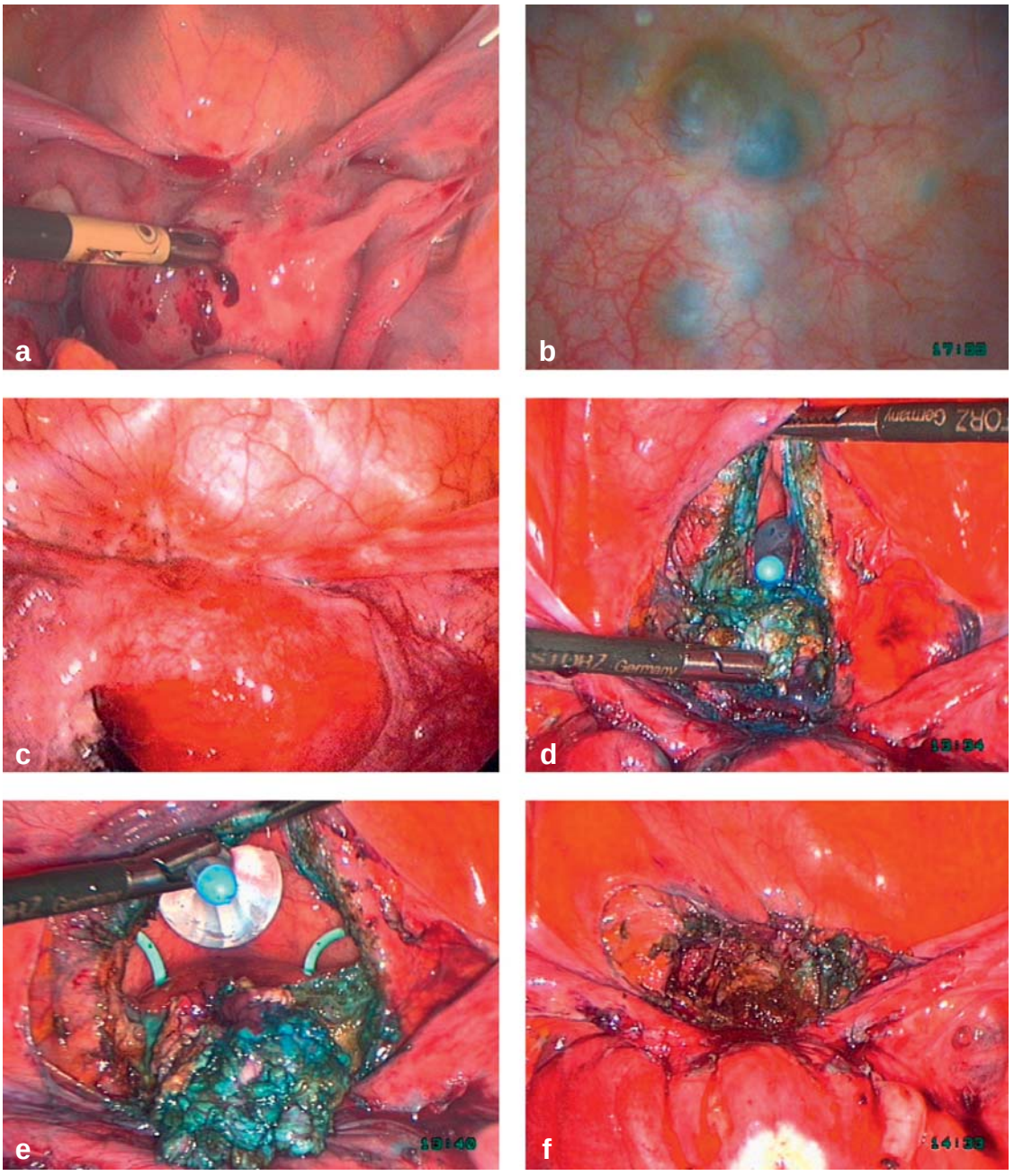
a) First, the focus of endometriosis is mobilized from the posterior fornix, and the rectum is mobilized. The vagina is temporarily closed. The focus is now located on the rectum within the abdominal cavity.

b) The uterus is transiently fixed to the abdominal wall to permit access to the area of operation.

c) The rectum, containing the focus of endometriosis, is now freed from tough, woodlike adhesions on both sides, removed from its enveloping myometrium with preservation of the adjacent nerves and vessels, and

d) separated from the invasive focus with a linear stapler in the typical manner.

e–h) With adequate mobilization of the descending colon, the rectum with the infiltrating focus in it can now be pulled in front of the vagina. The infiltrating focus is resected, the oral stump is prepared, and the stapler head is introduced. The stapler head is then brought back into the abdominal cavity, and the vagina is permanently closed. The laparoscopic anastomosis can now be performed in the typical manner through a transanal approach, and its functionality can be tested.



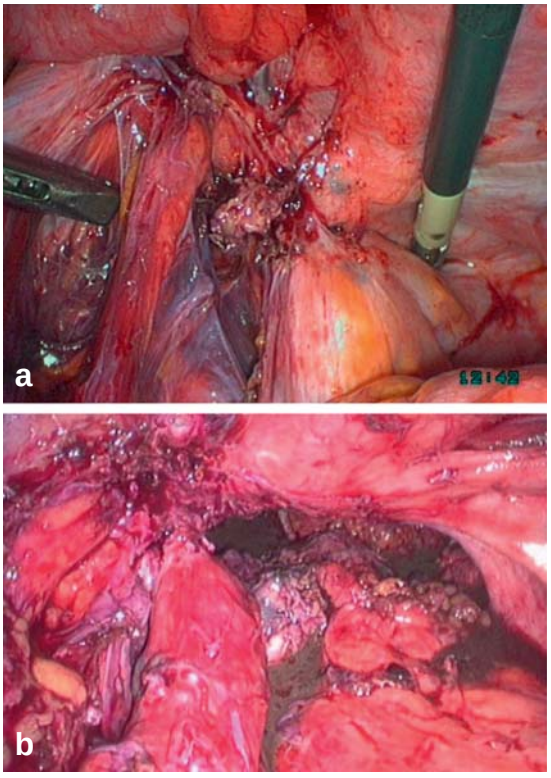
eFigure1: Endometriosis with transmural infiltration extending toward the urothelium

a) In a patient with endometriosis infiltrating the bladder, the round ligaments are pulled together in front of the uterus in a "V for victory" sign (24).

b) The picture reveals why a transurethral resection (TUR) is of no therapeutic benefit: the focus grows from the serous membrane of the bladder inward through the bladder wall, toward the urothelium.

c–d) Resection of the infiltrating endometriosis tissue from the roof of the bladder in a whetstone shape is usually unproblematic. Difficulty arises if the invasive focus extends deeply into the well-innervated vesical trigone.

e–f) The bladder wall can be closed safely through the laparoscope.



eFigure 2:
Extrinsic type of ureteric endometriosis

a) Involvement of the left ureter with endometriosis that also infiltrates the bowel and the right parametria (above), and
b) intrinsic endometriosis of the left ureter in a 30-year-old woman who already has one non-visualized kidney (below).